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# RAPID SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME NEW 2-AMINO-5-ALKYL/ARYL-1,3,4-THIADIAZOLES

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## ABSTRACT

Eight different 2,5-disubstituted 1,3,4-thiadiazoles have been prepared by conventional and microwave irradiation (MWI) methods using different aromatic or aliphatic carboxylic acids (**1**) and thiosemicarbazide (**2**). All the compounds have been prepared, purified and characterized by their spectral (IR, $^1$H NMR and Mass) data. The methods employed have been compared in terms of yields, reaction times. All the experimental conditions in MWI method, when compared to conventional, are easy, simple, eco-friendly and the reactions are rapid and high yield. All the compounds have been evaluated for their antimicrobial activity against *Staphylococcus aureus. Escherichia coli,* and *Pseudomonas aeugenosa.* Compounds showed mild to moderate activity, but not comparable with the standard (Oflaxacin).

**Key words**: 1,3,4-Thiadiazole, Microwave irradiation method, Rapid synthesis, Antimicrobial activity.

## INTRODUCTION

A recent literature survey revealed that the 1, 3, 4-thiadiazole moiety have been widely used by the medicinal chemist in the past to explore its biological activities. The development of 1, 3, 4-thiadiazole chemistry is linked to the discovery of Phenylhydrazines and hydrazine in the late nineteenth century. The first 1, 3, 4-thiadiazole was described by Fischer in 1882 but the true nature of the ring system was demonstrated first in 1890 by Freund and Kuh[1]. Members of this ring system have found their way in to such diverse applications as pharmaceuticals, oxidation inhibitors, cyanide dyes, metal complexing agents. The ending *-azole* designates a five membered ring system with two or more heteroatoms, one of which is nitrogen. The ending –ole is used for other five membered heterocyclic ring without Nitrogen. The numbering of monocyclic azole system begins with the heteroatom that is in the highest group in the periodic table and with the element of lowest atomic weight in that group. Hence the numbering of 1, 3, 4-thiadiazole is done in following manner. This designates that one sulphur group is present in the ring.

During recent years there has been intense investigation of different classes of thiadiazole compounds, many of which known to possess interesting biological properties such as antimicrobial[2], antituberculosis[3], anti-inflammatory[4], anticonvulsants[5], antihypertensive[6], antioxidant[7], anticancer[8] and antifungal[9] activity. Hence, this field has-ever-growing importance resulting in the development scores of thiadiazoles. Therefore, it has been considered worthwhile to synthesize some new 1,3,4-thiadiazole, by two different procedures i.e., conventional method and microwave irradiation (MWI) methods[10,11] for comparison, to characterize the new thiadiazoles by their analytical and spectral (IR, $^1$H NMR and mass) data.

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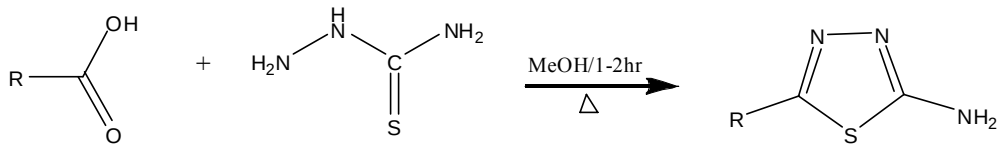
Aromatic or aliphatic carboxylic acids (1) and thiosemicarbazide (2) were subjected to conventional and MWI methods **(Scheme 1)**.



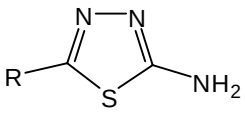

**1** **2** **3**

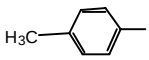
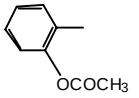
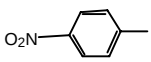
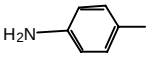
R = -H, -$CH_3$, $C_6H_5$,
$C_6H_4.NO_2$-4, $C_6H_4.CH_3$-4
$C_6H_4$.OH-2, $C_6H_4.NH_2$-4
$C_6H_4.OCOCH_3$-2,

**Scheme 1**

The product obtained in each of such reactions was purified and characterized as 2-Amino-5-alkyl/aryl-1,3,4-thiadiazoles. In MWI method, the reaction time was considerably reduced (6 min only) with increased percentage yields (70-90%) when compared with the conventional method. Physical data of new 1,3,4-thiadiazoles are presented in Table 1.

**Table 1: Physical data of 2-amino-5-alkyl/aryl-1,3,4-thiadiazoles (3a-h)**




| Compd. | R | m.p. ($^oC$) | % Yield | | Mol. formula | Mol. Wt. |
|---|---|---|---|---|---|---|
| | | | Conventional | MWI | | |
| **3a** | -H | 188-190 | 68 | 83 | $C_2H_3N_2S$ | 101 |
| **3b** | -$CH_3$ | 222-224 | 56 | 69 | $C_3H_5N_2S$ | 115 |
| **3c** |  | 220-222 | 61 | 86 | $C_8H_7N_2S$ | 177 |
| **3d** |  | 218-220 | 52 | 79 | $C_9H_9N_2S$ | 191 |
| **3e** |  | 156-158 | 56 | 64 | $C_8H_7N_2SO$ | 193 |
| **3f** |  | 168-170 | 64 | 84 | $C_{10}H_9N_2SO_2$ | 235 |
| **3g** |  | 258-260 | 62 | 90 | $C_8H_6N_3S\ O_2$ | 222 |
| **3h** |  | 170-172 | 48 | 69 | $C_8H_8N_3S$ | 192 |

## EXPERIMENTAL

Experimental procedures are given as general methods. All melting points were determined in open capillaries using Toshnwal melting point apparatus. Infra-red spectra of the compounds were recorded in KBr pellet using Shimadzu FTIR-8700 spectrometer, $^1$H NMR spectra on omega-500 MHz spectrometer using TMS as internal standard and mass spectra by the direct inlet method on VG micro mass 7070 H spectrometer operating at 70 eV.

**Synthesis of 2-amino-5-alkyl/aryl-1,3,4-thiadiazoles**

**General procedure**

**(A) Conventional method:** Appropriate aliphatic or aromatic carboxylic acid (0.05 M) and thiosemicarbazide (0.05 M) were taken into a RB flask and dissolved in alcohol (25 mL) by shaking. To this, concentrated sulphuric acid (10 drops) was added while shaking and the reaction mixture was heated under reflux for 1-2 hrs, on a hot water bath. After completion of the reaction (monitored by TLC) alcohol was removed to a possible extent by distillation and the residue was cooled and triturated with crushed ice. The product was filtered, washed with small portion of cold water and dried. It was purified by recrystallization from hot alcohol.

**(B) Microwave irradiation method:** Appropriate aliphatic or aromatic carboxylic acid (0.05 M) and thiosemicarbazide (0.05 M) were taken into a beaker and dissolved in minor quantity of dimethyl formamide (10 mL). To this solution concentrated sulphuric acid (10 drops) was added while stirring. A funnel was hanged in the beaker and covered with a watch glass. The reaction mixture was subjected to the microwave irradiation at 480 W for 3-6 min, with a pulse rate of 30 sec, each in a domestic LG little chef microwave oven. The solvent was removed by distillation and residue was cooled and triturated with crushed ice. The resultant product was filtered, washed with small portions of cold water and dried. It was purified by recrystallization from hot alcohol.

**Spectral characterization data of 1,3,4-thiadiazoles**

**Infrared spectrum of the compound (KBr, 3g):** has exhibited absorption characteristics of: 3218 (-$NH_2$), 3032 (C-H, aromatic), 1489 (C=C, aromatic) $cm^{-1}$, respectively

**$^1$H NMR spectrum of the compound ($CDCl_3$, 3g):** showed proton signals at: 7.22 (s, 2H, -$NH_2$ of thiadiazole), 7.55 to 8.02 (m, 4H, -Ar-H) δ, ppm, respectively.

**Mass spectrum (3g)** of the compound exhibited its molecular ion ($M^+$) at m/z 222.

Thus, based on the specified spectral data the compound has been characterized 2-amino-5-(4-nitro phenyl)-1,3,4-thiadiazole **(3g; R = $C_6H_4.NO_2$-4)**.

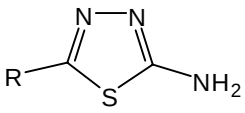
Adopting the above two procedures eight (8) different 2-amino-5-alkyl/aryl-1,3,4-thiadiazoles have been synthesized and characterized.

**Antimicrobial activity**

All the synthesized compounds have been screened for their antimicrobial activity by cup-plate[12] agar diffusion method by measuring inhibition in zone in mm. Ofloxacin (50 µg/mL) was used as a standard drug for antibacterial activity. The compounds were screened for their antibacterial activity against

*Staphylococcus aureus. Escherichia coli,* and *Pseudomonas aeugenosa* in neutrint agar medium. The sterilized agar media was poured into Petri dishes and allowed to solidify. On the surface of the media microbial suspension were spread with the help of sterilized triangular loop. A stainless steel cylinder of 8 mm diameter (pre-sterilized) was used to bore cavities. All the synthesized compounds (100 mg) were placed serially in the cavities with the help of micropipette and allowed to diffuse for 1.0 hr. Dimethyl sulfoxide (DMSO) was used as a solvent for all compounds and as a control. These plates were incubated at 37$^{o}$C for 34 hrs. the zone of inhibitions were observed around the cups and calculated. The results are presented in Table 2.

**Table 2: Antimicrobial activity of 2-amino-5-alkyl/aryl-1,3,4-thiadiazoles (3a-h)**




| S. No. | Sample code | *Staphylococcus aureus* | *Escherichia coli* | *Pseudomonas aeugenosa* |
|---|---|---|---|---|
| 1 | 3a | 08 | 10 | 10 |
| 2 | 3b | 10 | 10 | 11 |
| 3 | 3c | 11 | 11 | 12 |
| 4 | 3d | 12 | 13 | 11 |
| 5 | 3e | 11 | 10 | 12 |
| 6 | 3f | 15 | 12 | 13 |
| 7 | 3g | 12 | 15 | 11 |
| 8 | 3h | 13 | 12 | 13 |
| 9 | **Ofloxacin 50 µg/cup** | **18** | **18** | **16** |

Zone of Inhibition in mm

## RESULTS AND DISCUSSION

2-Amino-5-alkyl/aryl-1,3,4-thiadiazoles (yield 70-90%) could be successfully synthesized by using appropriate aliphatic or aromatic carboxylic acid and thiosemicarbazide. Among the two different experimental methods adopted: (a) Conventional method and (b) MWI method, a significant increase in yields with a shorter reaction times have been recorded in the latter (MWI) method, when compared with conventional methods, which involves longer reaction times under refluxing conditions with moderate yields. All the eight compounds **(3a-3h)** have been screened for their antimicrobial activity by cup-plate agar diffusion method by measuring the inhibition zone in mm. Ofloxacin (50 µg/mL) was used as a standard drug for antibacterial activity. The thiadiazole derivative **3f** having a 2-acetoxy phenyl group showed potent antibacterial activity against *S. aureus*, where as compound **3g** having 4-nitro phenyl group showed maximum inhibition against *E. Coli* and compounds **3f** and **3h** showed maximum antibacterial activity against *S. aerugenosa* with 2-acetoxy phenyl, 4-amino phenyl respectively. Rest of the compound showed mild to moderate antibacterial activity.

## CONCLUSIONS

The synthesis of 1,3,4-thiadiazole heterocycles that have been reported to date illustrates different approaches to the challenge of preparing these bioactive products and allows the synthesis of many novel chemical derivatives. In general, 1,3,4-thiadiazole derivatives are prepared by appropriate intra- or intermolecular ring closure reactions and the substituents are then modified as required. The area of the synthesis of 1,3,4-thiadiazole rings continues to grow, and the organic chemistry will provide more and better methods for the synthesis of this interesting heterocycle, allowing the discovery of new drug candidates more active, more specific and safer.

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